v. 4, n. 59, 2024

International Journal of Health Science

EXPLORING THE CONNECTION BETWEEN H. PYLORI INFECTION AND DEMENTIA RISK: AN UPDATED REVIEW

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Abstract: Objective: Explore the possible relationship between Helicobacter pylori infection and the risk of developing dementia, analyzing potential mechanisms and implications for prevention and management. **Methodology:** Bibliographic review that used the electronic database PubMed. Search terms included "Helicobacter Pylori", "H. pylori", "Campylobacter pylori", "Dementia" through the following search strategy: ("Helicobacter pylori" OR "H. pylori" OR "Campylobacter pylori") AND (Dementia). In the initial search 113 articles were found, however a total of 16 articles were selected for analysis in this review. **Revision:** The results reveal a significant correlation between the serointensity of H. pylori infection of specific strains and the risk of dementia, evidenced by the formation of pathogenic markers of Alzheimer's disease, malabsorptive syndrome, factors that are even more potentiated if co-infection with periodontal pathogens occurs. **Final considerations:** Therefore, the need for early detection of infectious risk factors in the prevention of dementia is highlighted. However, it is of fundamental importance to recognize the complexity of the topic and the need for more research to elucidate gaps in the pathophysiological mechanisms in which H. pylori can influence the development of dementia and thus, establish better prevention strategies in the population.

Keywords: Helicobacter Pylori, Campylobacter pylori, Dementia.

INTRODUCTION

Dementia is a major global health concern, significantly affecting cognitive function and quality of life for millions of people around the world. According to Piekut et al. (2022), it is estimated that dementia affects 4.7% of adults over 60 years of age, with an impactful annual number of 4.6 to 7.7 million cases, representing a substantial challenge for health

systems and the society. Recently, interest in infectious agents as potential contributors to the etiology of Alzheimer's disease and other dementias has grown among researchers. Among the relevant infectious agents, the bacterium Helicobacter pylori (Hp) has been highlighted. Doulberis et al. (2018) suggest that potential mechanisms of infection may include entry of the bacteria into the brain via the oral-nasal-olfactory route or through the circulation of infected monocytes, due to defective autophagy, which can compromise the blood-brain barrier and trigger neurodegeneration. This review seeks to provide valuable information about the possible relationship between Helicobacter pylori and dementia, opening new perspectives for understanding and managing this debilitating condition.

The origin of Alzheimer's disease (AD), the leading cause of dementia, has continued to be a topic of debate since its first description in 1906. Several hypotheses have been proposed to elucidate the etiology of AD, including the "amyloid cascade hypothesis." Although the pharmacological compounds developed based on this hypothesis did not achieve satisfactory results in clinical trials, they were fundamental in redirecting the hypotheses that seek to explain the genesis of AD (Frölich, 2020). Recent reports suggest that certain microorganisms, such as bacteria, may be associated with cognitive decline (Piekut et al., 2022). Currently, the pathophysiological connection between Helicobacter pylori infection and dementia is still uncertain (Albaret et al., 2020).

Additionally, the "microbial hypothesis" suggests that chronic infections with bacterial, viral and/or fungal pathogens may trigger the development of AD during aging through inflammatory processes. These pathogens, such as H. pylori, can invade the central nervous system (CNS) directly through the trigeminal nerve or the oral-olfactory route, or can act systemically through the gastrointestinal tract circulation. Research establishes the crucial role of the JAK/STAT signaling pathway as a key driver of neuroinflammation in the initiation of neurodegenerative diseases. (Kanspal et al., 2024).

Analyzing the influence of infectious agents and the inflammatory reaction to them in the context of dementia can help with early detection and the development of new treatment options. Therefore, the aim of this study is to explore the possible relationship between Helicobacter pylori infection and the risk of developing dementia, examining the potential mechanisms and their implications for the prevention and management of the disease.

METHODOLOGY

Bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. This strategy was used to develop the research through its guiding question: "Is there an association between Helicobacter pylori infection and an increased risk of developing dementia?" The searches were carried out through searches in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The search terms were used in combination with the Boolean terms "AND" and "OR" through the following search strategy: ("Helicobacter pylori" OR "H. pylori" OR "Campylobacter pylori") AND (Dementia). From this search 113 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles published in the period from 2019 to 2024 and which addressed the themes proposed for this research, studies of the type review, meta-analysis, studies. observational and experimental studies made available in

full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. After the initial screening, 45 articles were selected. applying the inclusion and exclusion criteria, 16 articles were selected to compose the collection of the present study.

DISCUSSION

Research into the relationship between Helicobacter pylori (Hp) infection and the risk of developing dementia reveals a complex and dynamic field of study. Understanding this potentially significant connection requires a comprehensive analysis of the underlying pathophysiological mechanisms and available epidemiological data. Known primarily for its association with gastrointestinal disorders, H. pylori infection is now emerging as a possible risk factor for neurological conditions, including dementia.

Studies exploring the effects of bacterial infection on brain metabolism, systemic inflammation, and pathological pathways that may contribute to neurodegeneration, however, despite promising findings, significant gaps remain in understanding the specific mechanisms through which H. pylori can influence the development of dementia. Continued investigation of this evidence is crucial to elucidate underlying mechanisms and develop effective prevention and treatment strategies for H. pylori-related dementia. According to Douros et al. (2024), studies on the possible link between clinically apparent Helicobacter pylori infection and the risk of developing Alzheimer's disease (AD) have brought to light relevant findings. Observations from preclinical, serological, and postmortem studies suggest that several infectious pathogens, including H. pylori, may play a crucial role in the development of AD. This association is reinforced by observational studies demonstrating a relationship between infectious disease burden and an increased risk of AD. Specifically, exposure to clinically apparent H. pylori was associated with a moderately increased risk of AD, with an odds ratio of 1.11, highlighting the potential relevance of this bacterial infection as a modifiable risk factor for AD. Interestingly, the increase in AD risk peaks at approximately 24% about a decade after the onset of clinically apparent H. pylori infection, suggesting a possible cumulative effect over time. The proposed link between H. pylori and the central nervous system adds a layer of complexity to this association, indicating possible mechanisms by which H. pylori can trigger neuroinflammation, neuronal damage, and neurodegeneration. Furthermore, the potential involvement of the gut-brain axis points to the complexity of the pathological pathways that can be activated by H. pylori infection, expanding the understanding of the relationship between gastrointestinal infections and brain health (Douros et al., 2024).

The study carried out by Beydoun et al. (2024) adopted a cross-sectional methodology with the aim of examining the relationship between seropositivity for Hp, the serointensity of antigens from this bacterium, the burden of persistent infections (CIP), and brain changes, including the volume and measurements of the brain structures evaluated. by magnetic resonance imaging (MRI). The results indicated a limited correlation between Hp seropositivity and the various volumetric outcomes measured by MRI. However, serointensity of various antigens revealed a range of imaging changes, establishing a clear relationship between Hp seropositivity, antigenic serointensity, CIP, and brain volumetric and structural measurements.

For Beydoun et al. (2020), co-infection between Hp and groups of periodontal pathogens emerges as a potential modulator in the early development of AD and all-cause dementia. This perspective is supported by recent studies that have investigated the effects of periodontal disease pathogens on brain health, highlighting the possibility of bacterial products crossing the blood-brain barrier and contributing to the pathogenesis of AD. Furthermore, evidence that the gram-negative bacterium Hp can have extradigestive effects, increasing the risk not only of AD but also of all-cause dementia and cognitive impairment, reinforces the need to investigate its interactions with periodontal pathogens. It is notable that infections with Hp and periodontal pathogens are more prevalent among minority groups compared to non-Hispanic whites, suggesting a possible role of these infections in the disparities observed in various neurodegenerative diseases among different ethnic groups. The analyzed study examined the synergistic effect of Hp seropositivity in conjunction with specific periodontal pathogens, revealing that certain pathogens, such as Prevotella intermedia (Pi), Campylobacter rectus (Cr), Factor 2 and the Orange-Red cluster, interact synergistically with seropositivity of Hp, increasing the risk of incident AD. Furthermore, the pathogen Actinomyces naeslundii (An) showed significant synergistic effects, especially among adults with higher titer levels, elevating the risk of all-cause dementia and AD. These findings provide robust evidence of an association between periodontal pathogens and dementia-related outcomes, especially among Hp-seropositive individuals. Such findings have important clinical implications for periodontists treating older adults and also point to a promising line of investigation into neurodegenerative processes, highlighting the importance of oral health in the prevention and management of dementia (Beydoun et al., 2020).

Furthermore, Beydoun et al. (2024) reported that their study is one of the few that correlates MR imaging findings with Hp and the serointensity of various Hp antigens. The research evaluated the serointensity of the Vacuolating cytotoxin A (VacA), Outer Membrane Proteins (OMP), GroEL and urease antigens, demonstrating that the serointensity of the VacA antigen is associated with the volumetric reduction of the putamen, the increase in the volume of hypersignal in the white matter in patients at average risk of developing AD. An association of OMP antigen serointensity with increased subcortical volume of the left putamen and worse white matter integrity in sites related to cognition was also observed. The serointensity of OMP, VacA and GroEL antigens showed an increase in mean diffusion and a reduction in fractional anisotropy in the superior and inferior cerebellar peduncle tracts. Additionally, a relationship was discovered between urease antigen serointensity and a reduced volume of the caudate nucleus in people with a higher genetic risk of developing AD.

According to Cárdenas, Boller and Román (2019), the evidence presented suggests a complex relationship between Hp infection and cognitive impairment in older adults. The results indicate that adults infected with cytotoxin A (cagA)-associated strains of Hp during the period 1988–1991 showed a significant increase in the level of cognitive impairment, as evidenced by low scores on the Mini-Mental State Examination (MMSE). Furthermore, older adults infected with Hp during the period 1999–2000 had lower Digital Symbol Summation Test (DSST) scores compared to those uninfected, indicating possible cognitive deficits associated with the infection. The quantitative summary of

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.1594592426066

seven studies suggests a weak but statistically significant association between Hp infection and dementia, although it is important to consider the complexity and heterogeneity of the included studies. These findings suggest that Hp may play a potential role as a risk factor for neurodegenerative diseases such as late-onset Alzheimer's disease (LOAD), affecting cognitive function through mechanisms including vascular damage and chronic inflammation. Furthermore, the association between impaired cognitive function and Hp infection appears to be stronger in certain demographic groups, such as US-born non-Hispanic white participants with more than 12 years of education, highlighting the need to consider sociodemographic factors in analyzing these associations (Cárdenas; Boller; Román, 2019).

The study conducted by Zilli et al. (2021), a longitudinal cohort study, aimed to analyze whether exposure to various pathogens, including Hp, modifies the risk of dementia, stating that no significant correlations were found between seropositivity for Hp and a higher risk of incidence of dementia. An important limitation of the study was the lack of knowledge about the use of medications by the participants. However, a great advantage of this study is the extensive number of participants analyzed in detail and continuously over several years (Zilli et al., 2021).

The relationship between Hp infection and the development of neurodegeneration in Alzheimer's disease has gained prominence in the scientific community. Understanding the biological mechanisms that link these two pathologies, one mainly impacting the gastrointestinal tract and the other the central nervous system, is crucial. According to recent studies, chronic Hp infection results in pathological changes in the mucosa of the gastrointestinal tract (Xie et al., 2023). These changes are attributed, in part, to outer membrane vesicles (OMVs) secreted by the bacteria, which have a known role in neuroinflammation, specifically in microglia and astrocytes (Doulberis et al., 2018). Xie et al. (2023) report that this neuronal inflammation occurs due to chronic exposure, with OMVs activating the complement system (C3-C3aR) and forming Aβ plaques, a pathogenic hallmark of Alzheimer's dementia.

Doulberis et al. (2018) add that extra-gastric systemic effects, due to the composition of vesicles, such as urease and GroEL, facilitate the transposition of the blood-brain barrier and increase the chemotaxis of pro-inflammatory cytokines in the central nervous system. Furthermore, OMVs can activate the transcription factor NF-kB, inducing the production of cytokines by astrocytes and microglia, such as IFNγ and IL-1β. The latter is implicated in the phosphorylation of tau protein and the formation of neurofibrillary tangles, typical in Alzheimer's disease (Kanspal et al., 2024; Doulberis et al., 2018). Studies such as those by Xie et al. (2023) and Doulberis et al. (2018) highlight the importance of Hp OMVs secreted in the gastrointestinal tract as the trigger for neuroinflammation that can trigger neurodegeneration.

The role of urease as a biological mechanism in Alzheimer's pathology was discussed. Kandpal et al. (2024) point out that this enzyme induces the production of inflammatory cytokines in microglial cells. Although it is not responsible for the change in the permeability of the blood-brain barrier in behavioral and object recognition studies, urease facilitates its passage to the CNS by producing ammonia, which alkalizes the stomach (Doulberis et al., 2018). Xie et al. (2023) explain that the barrier, composed of protective cells such as astrocytes and microglia, can be compromised during reactive astrocytosis, facilitating the development of Alzheimer's.

Research establishes the crucial role of the JAK/STAT signaling pathway as a key driver of neuroinflammation in the initiation of neurodegenerative diseases. The JAK/STAT cascade is an essential signal transduction pathway following H. pylori infection. At different sites in the brain, these signals activate cytokines, promote cellular inflammation and cause cell death, influencing myeloid cells and T cells towards pathogenic phenotypes, which may increase the amyloid cascade and elucidate the pathogenesis of Alzheimer's dementia (Kanspal et al., 2024).The JAK/STAT signaling pathway, an important biological mechanism in neuroinflammation, was studied in a control with drug-resistant Hp varieties, revealing the participation of STAT1 and STAT3 proteins, with the latter more related to the activation of genetic molecules in the pathogenesis of dementia (Zilli et al., 2021). Furthermore, Uberti et al. (2022) observed the activation of glycogen synthase kinase-3β (GSK-3β) upon bacterial infection, which resulted in an exaggerated phosphorylation of the tau protein. Additionally, Hp infection is associated with cobalamin malabsorption, which may contribute to reduced vitamin B12 levels associated with dementia. Nutritional deficiencies resulting from inflammation of the gastrointestinal tract caused by Hp can lead to malabsorptive metabolic syndromes, affecting the absorption of essential vitamins such as the aforementioned B12 and also folate.

These deficiencies can cause hyperhomocysteinemia, causing vascular disorders and cortical atrophy, a biological marker of cognitive changes in the CNS (Beydoun et al., 2024; Uberti et al., 2022). These findings reinforce the need for further research into the impact of Hp-induced hyperhomocysteinemia on neurodegeneration.

FINAL CONSIDERATIONS

This updated study explores the possible relationship between Helicobacter pylori infection and an increased risk of developing dementia. The results indicate a significant correlation between the serointensity of specific Hp strains and the risk of dementia, notably through pathogenic markers of Alzheimer's disease and the potentiation of these factors by co-infections with periodontal pathogens. Additionally, Hp infection is associated with cobalamin malabsorption, which may contribute to reduced vitamin B12 levels, also associated with dementia. These findings highlight the importance of early detection of infectious risk factors as a preventive strategy against dementia. However, the complexity of the pathophysiological mechanisms involved still requires further investigations to clarify how interactions between Hp and the neurological system can influence the development of neurodegenerative conditions. The research emphasizes the need for multidisciplinary approaches to establish effective strategies for preventing and managing dementia in the population, encouraging further studies to deepen the understanding and response to this worrying association. The complexity and severity of the implications found reinforce the message that gastrointestinal health may be intrinsically linked to cognitive health, shaping guidelines for future investigations and interventions.

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